

AMENDMENTS TO THE SPECIFICATION

Please replace the existing paragraph beginning at page 7, line 36, with the following rewritten paragraph:

--Figures 1A, 1B, 1C, 1D, 1E, and 1F. Top line: Nucleotide sequence of SEQ ID NO: 7, referred to herein as mNTPase or mCD39L4; bottom line: amino acid sequence of SEQ ID NO: 8, referred to herein as mNTPase or mCD39L4.--

Please replace the existing paragraph beginning at page 8, line 4, with the following rewritten paragraph:

-- Figures 2A, 2B, and 2C. Amino acid alignments of the full mNTPase (mCD39L4) amino acid sequence (SEQ ID NO:8) and the most closely related other NTPase proteins: garden pea NTPase (SEQ ID NO:10), potato apyrase (SEQ ID NO:11), yeast GDPase (SEQ ID NO:12). Identical residues are indicated by double underlining ~~dark background (white letters)~~, while conserved residues are indicated by single underlining ~~gray background~~. Alignments were made with pileup and boxshade from the Wisconsin Package Version 9.0, Genetics Computer Group (GCG), Madison WI.--

Please replace the existing paragraph beginning at page 8, line 14, with the following rewritten paragraph:

-- Figures 3A, 3B, 3C, and 3D. Alignment of 12 members of the NTPase (or CD39-like) gene family indicating the conserved apyrase regions I-IV. CD39=human (from Accession No. S73813; SEQ ID NO:13), ratCD39=rat (from Accession No. gi11754710; SEQ ID NO:14), CD39L1=human (Accession No. U91510; SEQ ID NO:15), ~~ChickATPase~~ ChiATPase=chicken (from Accession No. U74467; SEQ ID NO:16), peaNTPase=garden pea (from Accession No. P52914; SEQ ID NO:10), potRROP1=potato RROP1 gene (from Accession No. gi11381633; SEQ ID NO:11), yGDA1+y71KD=yeast genes (from Accession Nos. sp1P32621 + sp1P40009; SEQ ID NO:12), hCD39L2=CD39L2, celegans=C. Elegans gene (from Accession No. gi11086594; SEQ ID NO:17). Identical residues are indicated by double underlining ~~dark background (white letters)~~, conserved residues are indicated by single underlining ~~gray background~~. Alignments were made with pileup and boxshade from the Wisconsin Package 9.0, Genetics Computer Group (GCG), Madison, WI. Conserved portions of ACRs I-IV are boxed.--

Please replace the existing paragraph beginning at page 8, line 32, with the following rewritten paragraph:

-- Figures 4A, 4B, 4C, 4D, 4E, 4F, 4G, and 4H. Top line: Nucleotide sequence of SEQ ID NO:1, referred to herein as CD39L2; bottom line: amino acid sequence of SEQ ID NO:2, referred to herein as CD39L2.--

Please replace the existing paragraph beginning at page 8, line 36, with the following rewritten paragraph:

-- Figures 5A, 5B, 5C, 5D, and 5E. Comparison of the hydrophobicity predictions for the amino acid sequences of members of the human CD39-like gene family. Predictions were made using the Topred-II 1.1 program (Claros, M.G. & Von Hejine, G., 1994, Comput. Appl. Biosci. 10:685-686; putative setting=0.5; certain setting=1.0).--

Please replace the existing paragraph beginning at page 9, line 5, with the following rewritten paragraph:

-- Figures 6A, 6B, 6C, 6D, 6E, 6F, 6G, and 6H. Top line: Nucleotide sequence of SEQ ID NO:3, referred to herein as CD39L3; bottom line: amino acid sequence of SEQ ID NO:4, referred to herein as CD39L3.--

Please replace the existing paragraph beginning at page 9, line 9, with the following rewritten paragraph:

-- Figures 7A, 7B, 7C, 7D, 7E, and 7F. Top line: Nucleotide sequence of SEQ ID NO:5, referred to herein as CD39L4; bottom line: amino acid sequence of SEQ ID NO:6, referred to herein as CD39L4.--

Please replace the existing two (2) paragraphs beginning at page 9, line 13, with the following two (2) rewritten paragraphs:

-- Figures 8A, 8B, 8C, and 8D. Amino acid alignments of the full-length protein sequences for human members of the CD39-like gene family. CD39 (from Accession No. S73813; SEQ ID NO:13), CD39L1 (from Accession No. U91510; SEQ ID NO:15), CD39L2 (it is noted that the CD39L2 polypeptide illustrated here depicts a derived amino acid sequence that is encoded from the ATG codon beginning at nucleotide 148 (see FIG. 4A) and, therefore, includes an additional 28

amino acid residues N-terminal to those depicted in FIG. 4A; this form of CD39L2 is also intended to be included within the scope of the present invention), CD39L3, CD39L4.

Identical residues are indicated by double underlining ~~a black background (white letters)~~, and conserved residues are indicated by single underlining ~~a gray background~~. Spaces in the sequences are indicated by a dash-dot. Apyrase regions (ACRs) are indicated by arrows, with conserved portions of ACRs I-IV are highlighted by the boxed sections. Alignments were made using pileup and boxshade from the Wisconsin Package Version 9.0 Genetics Computer Group (GCG), Madison, WI.--

Please replace the existing paragraph beginning at page 9, line 33, with the following rewritten paragraph:

-- Figures 9A, 9B, 9C, 9D, and 9E. Amino acid sequence of dCD39L4 ("dNTPase"; SEQ ID NO:9) and alignment of the amino acid sequence with the most closely related members of the CD39-like gene family. peaGDP, garden pea NTPase (from Accession No. P52194; SEQ ID NO:10); ptoapryase, potato RROP1 gene (from Accession No. gi11381633; SEQ ID NO:11); CD39L2; CD39L4, and yGDPase, yeast yGDA1 gene (from Accession No. sp1P32621; SEQ ID NO:12). Apyrase regions (ACRs) are indicated by arrows, with conserved portions of ACRs I-IV are highlighted by the boxed sections.--

Please replace the existing paragraph beginning at page 96, line 13, with the following rewritten paragraph:

-- First, a novel murine family member was cloned by low stringency screening of mouse cDNA libraries with a human CD39L1 cDNA clone (Chadwick, B.P. & Frischauf A.-M., 1997, Mamm. Genome 8:668-672). A 1738 bp cDNA clone was isolated from an adult mouse testis cDNA library (Stratagene Ltd., Cambridge, UK) and sequenced. DNA sequence comparisons with the human CD39L1 cDNA sequence showed moderate DNA homology of approximately 39% identity). An open reading frame (ORF) could be detected for the cDNA sequence, but indicated that the cDNA clone did not contain the initiation methionine codon and, therefore, did not extend to the 5' end. Database searches with the mouse cDNA sequence identified two mouse EST clones that extended the cDNA sequence at the 5' end (Accession Nos. AA116990 and AA120757). The EST clones were resequenced. The cloned and the resequenced nucleotide sequences were analyzed

and were combined appropriately to yield the nucleotide sequence (SEQ ID NO:7) depicted in FIGs. 1A, 1B, 1C, 1D, 1E, and 1F, and referred to herein as mCD39L4 or mNTPase. The sequence revealed an ORF from nucleotides 205 to 1599 with the ATG at nucleotide 205 having a moderate match to the initiation start site for vertebrates (AAGAAUAUGG (SEQ ID NO: 18) for mNTPase versus GCCGCCAUGG (SEQ ID NO: 19); Kozak, M., 1989, J. Biol. Chem. 108:229-241). The derived amino acid sequence is also shown in FIGs. 2A, 2B, and 2C (SEQ ID NO:8). No apparent polyadenylation signal existed, although the cDNA clone isolated contained a poly-A tail.--

Please replace the existing three (3) paragraphs beginning at page 97, line 9, with the following three (3) paragraphs:

-- Database searches with the derived amino acid sequence identified homology with other members of the NTPase family. FIGs. 2A, 2B, and 2C ~~show~~ ~~shows~~ an alignment of the full mNTPase (mCD39L4) protein sequence against three of the most homologous known NTPases, from garden pea, potato and *Saccharomyces cerevisiae*. The mNTPase protein shares approximately 30% amino acid identity with the three other NTPases.

The region of highest homology between all members of the NTPase family is at the amino terminus of the protein. Handa & Guidotti (Handa, M. & Guidotti, G., 1996, Biochem. Biophys. Res. Commun. 218:916-923) highlighted four regions of NTPases referred to as putative apyrase-conserved regions ("ACRs"). FIGs. 3A, 3B, 3C, and 3D ~~show~~ ~~shows~~ an alignment of ACRs I-IV. (See Section 3, Section 5, and its subsections, above, for a delineation of the amino acid residues that make up ACRs I-IV of the CD39-like polypeptides of the invention.) ACR conservation would indicate that these regions are essential for the functioning of the protein, while changes in the regions surrounding these domains can be tolerated. The presence of all four ACRs in the mNTPase (mCD39L2) indicates that mNTPase is a new member of the NTPase family.

BLAST searches with the DNA sequence of mNTPase (mCD39L4) revealed two overlapping human EST clones with 57% DNA sequence identity to portions of mNTPase (Accession Nos. H08436 and AA378537). Upon combination and analysis of the resulting sequence, an ORF was identified that showed homology to NTPases. The putative NTPase protein sequence, referred to herein as "CD39L2," is shown in FIGs. 3A, 3B, 3C, and 3D alongside the other NTPase protein sequences. The identification and characterization of the full-length CD39L2 polypeptide and nucleotide sequences is described in the Example presented in Section 7, below.--

Please replace the existing two (2) paragraphs beginning at page 101, line 8, with the following two (2) rewritten paragraphs:

-- Identification of partial human CD39L2 sequence was described in the Example presented in Section 6, above. The CD39L2 insert was used to isolate additional clones from a human adult breast epithelial cDNA library (ZR75), a human T-leukemia cell line J6 cDNA library (Jurkat), and a human keratinocyte stem cell cDNA library (KER). Of 23 cDNA clones that were isolated and sequenced, all but one appeared to be alternatively spliced or unspliced. Within the 2762 bp cDNA that appeared to be neither unspliced or alternatively spliced, an ORF extending to nucleotide 1600 containing ACRs I-IV was identified. Two ATG codons with a poor match to the consensus translation initiation site were found at nucleotide positions 148 and 232 (AUGUGAAUGA (SEQ ID NO: 28) at 148 and ACAAGGAUGA (SEQ ID NO: 29) at 232 versus consensus GCCGCCAUGG (SEQ ID NO: 19); Kozak, M., 1989, J. Biol. Chem. 108:229-241). Based on homology to mNTPase, the ATG at nucleotide position 232 is the initiation codon. (See FIGs. 9A, 9B, 9C, 9D, and 9E for a depiction of the CD39L2 amino acid sequence that results from translation from the upstream, position 148, start codon; such a form of CD39L2 as well as nucleotide sequences that encode this form of the polypeptide are also intended to be included as part of the present invention.) A single polyadenylation signal of AAUAAA (SEQ ID NO: 30) was identified at nucleotide position 2700, 22 nucleotides 5' of the poly(A) tail of the human CD39L2 cDNA.

The nucleotide sequence (SEQ ID NO:1) and derived amino acid sequence (SEQ ID NO:2) of human CD39L2 is depicted in FIGs. 4A, 4B, 4C, 4D, 4E, 4F, 4G, and 4H. Hydrophobicity plots using Topred-II 1.1 (Claros, M.G. & Von Hejine, G., 1994, Comput. Appl. Biosci. 10:685-686) predicted a single transmembrane segment at the N-terminal extreme of the protein, suggesting that CD39L2 has a short putative cytoplasmic tail and a large extracellular C-terminal domain (FIG. 5C). There are two potential N-glycosylation sites in the predicted extracellular domain. A cAMP and cGMP-dependent protein kinase and a protein kinase-C phosphorylation site are found directly after the initiation methionine codon (nucleotide 232).--

Please replace the existing paragraph beginning at page 102, line 19, with the following rewritten paragraph:

-- A 1669-bp ORF was identified within the cDNA insert. The nucleotide sequence (SEQ ID NO:3) and derived amino acid sequence (SEQ ID NO:4) of the cDNA insert, referred to herein as CD39L3, are shown in FIGs. 6A, 6B, 6C, 6D, 6E, 6F, 6G, and 6H. The amino acid sequence was

revealed to contain ACRs I-IV, an ATG codon at position 83, and a single polyadenylation signal at position 2758. Hydrophobicity plots as described above predict two potential transmembrane segments at the N and C-terminal extremes of the protein (FIG. 5D). There are seven potential extracellular N-glycosylation sites. A cAMP- and cGMP- dependent protein kinase site and a protein kinase-C phosphorylation site are located at the C-terminal extreme of the protein.--

Please replace the existing two (2) paragraphs beginning at page 103, line 16, with the following two (2) paragraphs:

-- The nucleotide sequence (SEQ ID NO:5) and derived amino acid sequence (SEQ ID NO:6), referred to herein as CD39L4, is depicted in FIGs. 7A, 7B, 7C, 7D, 7E, and 7F. The sequence contained a poly(A)tail, but no consensus polyadenylation sequence (Proudfoot, 1991, New Biol. 3:851-854). This is also the case for mNTPase. Hydrophobicity plots as described above predicted a single transmembrane segment at the N-terminal extreme of the protein (Fig. 5E). This is similar to the predicted topology of CD39L2 and different from that of CD39, Cd39L1, and CD39L3. There are three potential extracellular N-glycosylation sites.

FIGs. 8A, 8B, 8C, and 8D depicts an alignment of each of the above-described sequences, along with other members of the NTPase CD-39-like gene family. The ACR domains are indicated by arrows.--

Please replace the existing paragraph beginning at page 105, line 31, with the following rewritten paragraph:

-- The predicted amino acid sequence of the *D. melanogaster* CD39-like gene, referred to herein as dCD39L4, containing the ACRs-I-IV was shown in FIGs. 9A, 9B, 9C, 9D, and 9E, aligned against the gene family members with the highest homology. Three N-glycosylation consensus sites were found in the putative extracellular domain, and two potential cAMP- and c-GMP-dependent protein kinase phosphorylation sites were found in the putative N-terminal cytoplasmic domain. Hydrophobicity plots as described above predicted a single transmembrane segment at the N-terminal extreme of the dCD39L4 protein. The topology of dCD39L4 is therefore most similar to the predicted topology of the CD39L2 and Cd39L4 proteins.--

AMENDMENTS TO THE DRAWINGS

Please replace the drawings with the attached formal drawing sheets (forty-six (46) different sheets, Figs. 1A-9E) submitted herewith.